DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Se

Food and Drug Admin.
Rockville MD 20857

IND 25,512

Roberts Laboratories Inc.
Attention: David Haenick, Ph.D.
4 Industrial Way West
Eatontown, NJ 07724-2274

Dear Dr. Haenick:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Emitasol (metoclopramide) Nasal Spray.

We also refer to your amendment, which requested Agency review of Protocol 25,512-301R entitled, "Comparison of the Efficacy and Safety of Emitasol Nasal Spray Versus Placebo in Patients With Diabetic Gastroparesis." In this Phase III study, 200 patients will be randomized to metoclopramide nasal spray, 10 mg or 20 mg administered four times daily (first study phase). After four weeks, patients will be re-randomized to metoclopramide nasal spray, 10 mg, 20 mg, or placebo administered four times daily (second study phase) (Note: A modified version of this protocol was discussed at the End of Phase II meeting held between representatives of your firm and this Division.)

We have completed our review of the clinical portion of your submission and have the following recommendations for protocol modifications:

1. We recommend a placebo arm in phase one of the study. In the absence of a meaningful and statistically significant dose response in phase one, the efficacy of study drug cannot be established and the second phase results may not be adequate to support approval. Analysis of the first study phase may include treatment failure/withdrawal due to lack of efficacy as a endpoint as well as results of the symptom assessment questionnaire (SAQ). The efficacy results in the second study phase may be enriched by the absence of the dropouts from phase one. Efficacy in the phase one intention to treat population is needed to support efficacy in phase two. It may be necessary to drop the placebo arm after phase one. For additional comments on this issue, refer to the Division's response to clinical question #3 in the meeting minutes.

2. A global assessment of therapy should be added to support the results of the SAQ.

3. Efficacy trends in multiple symptomatic parameters would be important to support any statistically significant result that may depend on single or redundant symptoms. This is particularly true if the reflux type symptoms predominate in the differences between groups.

4. The proposed scratch off laminate label containing the identity of the assigned treatment produces a potential for unblinding that may be easily avoided by eliminating this portion of the label.

5. Pr tocol deviations/violations and what violations will warrant exclusion from analysis should be stated before beginning the study.

6. Analysis of dropouts due to lack of efficacy should be included in the efficacy assessment.

7. The definition of the intention to treat populations should be clearly stated.

If you have any questions, contact Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310

Sincerely yours,

Lilia Talarico MD

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